

[0276] In another embodiment, the invention is implemented primarily in hardware using, for example, hardware components such as application specific integrated circuits (ASICs). Implementation of the hardware state machine so as to perform the functions described herein will be apparent to one skilled in the relevant art(s).

[0277] In yet another embodiment, the invention is implemented using a combination of both hardware and software.

[0278] In one example embodiment, the present invention can be implemented in a computer-based monitor unit for use in a clinical setting. In another embodiment, the present invention can be implemented in an ambulatory unit akin to a Holter monitor, personal computing device, or similar portable device. In yet another embodiment, the present invention can be implemented in an implantable medical device such as an implantable cardioverter defibrillator (ICD).

[0279] In summary, the approach described herein met the objectives of: 1) introduce a set of metrics designed to probe the degree of sinus rhythm fragmentation; 2) test the hypothesis that the degree of fragmentation of heartbeat time series increases with the participants' age in a group of healthy subjects; 3) test the hypothesis that the heartbeat time series from patients with advanced coronary artery disease (CAD) are more fragmented than those from healthy subjects; and 4) compare the performance of the new fragmentation metrics with standard time and frequency domain measures of short-term HRV. The methods used in the approach described herein included: analysis of annotated, open-access Holter recordings (University of Rochester Holter Warehouse) from healthy subjects and patients with CAD using these newly introduced metrics of heart rate fragmentation, as well as standard time and frequency domain indices of short-term HRV, detrended fluctuation analysis and sample entropy. The results of the approach described herein included the following. The degree of fragmentation of cardiac interbeat interval time series increased significantly as a function of age in the healthy population as well as in patients with CAD. Fragmentation was higher for the patients with CAD than the healthy subjects. Heart rate fragmentation metrics outperformed traditional short-term HRV indices, as well as two widely used nonlinear measures, sample entropy and detrended fluctuation analysis short-term exponent, in distinguishing healthy subjects and patients with CAD. The same level of discrimination was obtained from the analysis of normal-to-normal sinus (NN) and cardiac interbeat interval (RR) time series. Conclusions of the approach described herein included the following. The fragmentation framework and accompanying metrics introduced here constitute a new way of assessing short-term HRV under free-running conditions, one which appears to overcome salient limitations of traditional HRV analysis. Fragmentation of sinus rhythm cadence may provide new dynamical biomarkers for probing the integrity of the neuroautonomic-electrophysiologic network controlling the heartbeat in health and disease.

[0280] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art (including the contents of the documents cited and incorporated by reference herein), readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such

adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance presented herein, in combination with the knowledge of one skilled in the art.

[0281] While various embodiments of the present invention have been described above, it should be understood that they have been presented by way of example, and not limitation. It will be apparent to one skilled in the relevant art(s) that various changes in form and detail can be made therein without departing from the spirit and scope of the invention. Thus, the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

What is claimed is:

1. A method of assessing cardiovascular risk of a subject, comprising:

receiving a first set of electrocardiogram (ECG) signals of the subject;

analyzing data from the first set of ECG signals to identify sign changes in heart rate

acceleration in the first set of ECG signals;

determining a degree of fragmentation in the first set of ECG signals based on the identified sign changes in heart rate acceleration; and

assessing cardiovascular risk of the subject based on the degree of fragmentation.

2. The method of claim 1, wherein analyzing data from the first set of ECG signals further comprises:

deriving, from each ECG signal, a time series of normal-to-normal (NN) intervals,  $\{NN_i\}=\{t_{N_i}-t_{N_{i-1}}\}$ , wherein  $t_{N_i}$  represents the time of occurrence of the  $i^{th}$  normal sinus beat, and the time series of the differences between consecutive NN interval increments,  $\{\Delta NN_i\}=\{NN_i-NN_{i-1}\}$ ; and

computing a set of fragmentation indices from the time series derived from each ECG signal.

3. The method of claim 2, wherein a fragmentation index in the set of fragmentation indices comprises: a percentage of zero-crossing points in the time series of the NN intervals or a percentage of inflection points (PIP) in the time series of the NN intervals.

4. The method of claim 2, wherein a fragmentation index in the set of fragmentation indices comprises an inverse of an average length of acceleration and deceleration NN segments ( $1/ALS_{NN}$ ), wherein the acceleration and deceleration segments are sequences of NN intervals between consecutive inflection points for which the differences between two NN intervals are  $<0$  and  $>0$ , respectively, and wherein a length of a segment is the number of NN intervals in the segment.

5. The method of claim 2, wherein a fragmentation index in the set of fragmentation indices comprises: a percentage of short NN segments ( $PSS_{NN}$ ), wherein  $PSS_{NN}$  further comprises a complement of a percentage of NN intervals in acceleration and deceleration segments with three or more NN intervals.

6. The method of claim 2, wherein a fragmentation index in the set of fragmentation indices comprises: a percentage